IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 9032
VAN MEEL	Art Unit: 1655
Appl. No. 09/891,873	Examiner: Meyers, Carla J.
Filed: June 26, 2001	Atty. Docket: 0652.2300001/EKS/PSC/TAC
For: **Method for Monitoring the Effect of Cancer Therapies**	

Amendment and Reply Under 37 C.F.R. § 1.111

Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Office Action dated **January 10, 2002**, Applicant submits the following Amendment and Remarks. This Amendment is provided in the following format:

(A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;

(B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and

(C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R.

§ 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Specification:

Please substitute the pending paragraph beginning on page 2, line 24, with the following paragraph:

B1

Consequently, chemical compounds that inhibit the tyrosine kinase activity of the growth factor receptors, antibodies directed to the extracellular domain of a growth factor receptor or the growth factors (or active fragments thereof) themselves have been suggested for the therapy of aberrant proliferation (Pharmacol. Ther. 82, 241, 1999). In addition, compounds that interfere with components of the deregulated intracellular signal transduction pathway downstream the receptor tyrosine kinase activity, e.g. inhibitors of components of the Ras pathways (i.e. farnesyl transferase inhibitors) or of the MAP kinase pathways (i.e. MEK or src kinase inhibitors) are suitable for therapeutic treatment of malignancies. In the following, the term "growth factor cancer drugs" is used as a synonym for compounds that act by a mechanism defined above.

Please substitute the pending paragraph beginning on page 6, line 3, with the following paragraph:

B2 It has been found in the present invention that the tumor cell growth modulating effects of growth factor cancer drugs can be monitored by determining the change in telomerase activity in cancer tissues/cells evoked by these drugs. Thus, telomerase activity can be utilized as a so-called "surrogate marker" for antitumor efficacy of these drugs.

Please substitute the pending paragraph beginning on page 11, line 23, with the following paragraph:

B3 As growth factor cancer drugs, the compounds designated "Inhibitor 1" and "Inhibitor 2" were administered, which belong to the class of pyrimido-pyrimidines and which are selective for the EGF tyrosine kinase receptor. "Inhibitor 1" is 4-((3-chloro-4-fluoro-phenyl)amino)-6-(1-methyl-4-piperidinyl-amino)-pyrimido(5,4d)pyrimidine; "Inhibitor 2" is 4-((3-chloro-4-fluoro-phenyl)amino)-6-(4-amino-4-methyl-1-piperidinyl)-pyrimido(5,4d)pyrimidine.

In the Claims:

Please replace pending claim 11 with the following claim 11:

B4 11. (Twice Amended) The method of claim 1, wherein the growth factor cancer drug is an inhibitor of an enzymatic protein of a MAP kinase pathway.

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, Claims 1-13 and 17 are pending in the application, with Claim 1 being the sole independent claim. Claim 11 has been amended to more particularly point out what Applicants regard as the invention and to make explicit that which was implicit in the original claim. Support for the amended claim may be found, for example, in the specification at Page 2, lines 14-19. The amendment does not introduce new matter. Accordingly, entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Specification

The Examiner has stated that the position and the direction of the quotes should be corrected. Applicants have reviewed the specification for occurrences of this typographical error and have amended the specification according to the Examiner's suggestion. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1-4, 6-13 and 17 under 35 U.S.C. § 112, first paragraph, because the specification allegedly "does not reasonably provide enablement for methods which monitor and evaluate the efficacy of any growth factor cancer drug by detecting a change in the level of telomerase activity in cells treated with said drug." Paper No. 6, page 2. Specifically, the Examiner has stated that:

> [T]he specification and the prior art do not teach that all "growth factor cancer drugs" act via a mechanism which includes inhibition of telomerase activity. The specification provides no information regarding the effect of inhibitors of EGF, IFG, PDGF, neurotrophic factors, components of the MAP kinase pathway, MEK or src on telomerase activity. The findings obtained with EGF, TGF-β1 and NGF cannot be extrapolated to all growth factors or to all compounds which alter any signaling mechanism associated with a growth factor. Insufficient evidence has been provided to support the conclusion that altering the signaling pathway of any growth factor results in an inhibition in telomerase activity and an associated inhibition in cancer cell growth.

(*Id* at page 3.). Applicants respectfully disagree with the Examiner's rejection. Specifically,

Applicants note that the claims are directed to a *method* of monitoring and evaluating the efficacy of a growth factor cancer drug in a patient by correlating telomerase activity with the therapeutic effect of said growth factor cancer drug. Therefore, it is not necessary to provide evidence that all growth factor cancer drugs or all compounds, which alter any signaling mechanism associated with a growth factor, result in an inhibition in telomerase activity. Indeed, the purpose of the method is to determine whether and to what extent a growth factor cancer drug has, at a given dosage, an effect on telomerase activity. If the administration of a compound, at the dosage of interest, results in a reduction of telomerase

activity, then the method is suitable to monitor the therapeutic effect of that compound in the given therapeutic setting. However, if a growth factor cancer drug does not, at a given dosage, have an effect on telomerase activity, it may be concluded that either the chosen dosage is not suitable to achieve a therapeutic effect, or, alternatively, the method is not appropriate for this particular scenario, *i.e.* with regard to the individual to be treated or to the particular tumor type.

Because the claimed method does not require that all growth factor cancer drugs have the effect of reducing telomerase activity nor requires that such a drug is active over a broad dosage range, the fact that applicants have not shown that all growth factor cancer drugs have such activity is irrelevant. The essential point of the method is to determine and monitor, in a given therapeutic setting, the effect of a growth cancer drug on telomerase activity and to correlate a reduction of telomerase activity with the therapeutic benefit of the drug.

As disclosed in the specification (page 11, line 23 through page 12, line 8), a number of growth factor cancer drugs that interact with tyrosine kinase receptors do result in the reduction of telomerase activity. It is likely that these growth factor cancer drugs mediate the reduction of telomerase activity by interfering with components of the signal transduction pathways downstream of tyrosine kinase activity. It is, therefore, reasonable to expect that the majority of growth factor cancer drugs that act interact with tyrosine kinase receptors will reduce telomerase activity by interfering with components of the signal transduction pathways downstream of tyrosine kinase activity. The Examiner has not provided evidence for why one would not expect the majority of growth factor cancer drugs that act by this mechanism to reduce telomerase activity. Given the high level of skill in the

art and teachings in the specification as to methods to assay for telomerase activity, it would be a simple matter of routine experimentation for one of ordinary skill in the art to determine which growth factor cancer drugs actually reduce telomerase activity and to correlate this activity with therapeutic effect.

One factor to be considered in determining whether undue experimentation is required is "the amount of direction or guidance presented" *See Wands* 8 USPQ2d 1400 at 1404. In the present application, clear guidance on how to determine the level of telomerase activity is given, and the tools for carrying out these assays were readily available. A variety of assays for determining the level of telomerase activity are disclosed in the specification, *e.g.*, at page 8, line 16 through page 9, line 18. These assays, and the techniques required are routine, and can be practiced easily by one of ordinary skill in the art. The specification further discloses how to compare levels of telomerase activity before and during and/or after treatment through the use of historical controls and by comparison to standard levels of telomerase activity, depending on tumor types and clinical stage of the diseases. See, *e.g.*, page 9, line 19-26. Additionally, the specification discloses a method for determining the level of telomerase activity in cell samples of cancer patients during therapy in order to optimize therapeutic benefit to the patient.

With respect to the Examiner's statement that "[i]nsufficient evidence has been provided to support the conclusion that altering the signaling pathway of any growth factor results in an inhibition in telomerase activity and an associated inhibition in cancer cell growth" (Paper No. 6, sect. 2, p. 3), Applicants again reiterate that the claims do not require that the growth factor cancer drug have any effect on telomerase activity. However, if said growth factor does have an effect on telomerase activity as determined by the methods

taught in the specification, it would be reasonable to correlate this inhibitory effect with an inhibition of tumor/cancer cell growth. *See* Specification, page 3, lines 14-28.

In view of the above, Applicants assert that it would not require undue experimentation to practice the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

II. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-13 and 17 under 35 U.S.C.§112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Paper No. 6, page 4. The Examiner asserted that "claims 1-13 and 17 are indefinite over the recitation of 'growth factor cancer drug'" and that "the specification discusses growth factor drugs but does not provide a complete and fixed definition for this phrase." (Paper No. 6, sect. 3, p. 4). Applicants respectfully disagree.

The test for indefiniteness is whether the scope of the claim is clear to a hypothetical person possessing an ordinary level of skill in the pertinent art. *See* M.P.E.P. § 2171 (7th ed., Rev. 1, Feb. 2000). The language of the claim must reasonably apprize those skilled in the art of both the utilization and the scope of the invention. *See PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558 (Fed. Cir. 1996).

The specification does provide a complete and fixed definition of "growth factor drugs" which reasonably apprizes those skilled in the art of both the utilization and the scope of the invention. Specifically, the specification states:

> Consequently, chemical compounds that inhibit the tyrosine kinase activity of the growth factor receptors, antibodies directed to the extracellular domain of a growth factor receptor or the growth factors (or active fragments thereof) themselves have been suggested for the therapy of aberrant proliferation (Pharmacol. Ther. 82, 241, 1999). In addition, compounds that interfere with components of the deregulated intracellular signal transduction pathway downstream the receptor tyrosinase kinase activity, e.g. inhibitors of components of the Ras pathways (i.e. farnesyl transferase inhibitors) or of the MAP kinase pathways (i.e. MEK or src kinase inhibitors) are suitable for therapeutic treatment of malignancies. In the following, the term "growth factor cancer drugs" is used as a synonym for compounds that act by a mechanism defined above.

Page 2, line 24 through page 3, line 5. Examples of growth factor drugs whose efficacy may be monitored by the method of the invention are also disclosed in the specification, *e.g.*, at page 6, line 19 through page 7, line 7.

The Examiner has asserted that "claims 1-13 and 17 are indefinite over the recitation of 'component of a MAP kinase pathway.'" (Paper No. 6, sect. 3, p. 4.) Applicants respectfully disagree. The specification refers to the MAP kinase pathway as a "number of enzymatic reactions." Specifically, the specification states:

> Upon binding of a growth factor to its respective receptor, the receptor transmits a signal from its extracellular domain across the plasma membrane to the cytoplasmic domain, to which a tyrosine kinase activity is associated. Activation of the tyrosine kinase triggers a number of enzymatic reactions (via the Ras pathways or MAP kinase pathways) and biological effects, ultimately leading to DNA synthesis and cell proliferation.

(Page 2, lines 14-19). Specific enzymatic proteins that are components of the MAP kinase pathway are listed, including MEK and src kinase. (*See* Page 3, line 2.) However, solely to expedite allowance of the claims, and not in acquiescence to the Examiner's rejection,

claim 11 has been amended to clarify that the recited growth factor cancer drug is an inhibitor of "an enzymatic protein" of a MAP kinase pathway.

Applicants submit that all of the claims are clear and definite. Accordingly, withdrawal of the rejection is respectfully requested.

III. Claim Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-4, 6, 8, 10, 11 and 17 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harley (U.S. Patent 5,863,726) in view of Zhu *et al.*, *Proceedings of the National Academies of Sciences, USA* (93):6091-6095 (1996). The Examiner has also rejected claims 1-3 and 17 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harley (U.S. Patent 5,863,726) in view of Sigala *et al., Clinical Cancer Research,* 5:1211-1218 (1999). In order to establish a *prima facie* case of obviousness, the Examiner must establish that there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In addition, the Examiner must demonstrate that there is a reasonable expectation of success. Furthermore, the teaching or suggestion to make the claimed combination must both be found in the prior art, and not be based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* MPEP § 2142. In the instant rejection, the Examiner has not established a suggestion or motivation to make the claimed combination in the prior art, nor has the Examiner demonstrated a reasonable expectation of success. The Examiner only states that it would be "obvious" to cure the defects of one reference with the teachings of the other

reference. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness over Harley in view of Zhu *et al.* and Harley in view of Sigala *et al.*. Accordingly, the Examiner is respectfully requested to reconsider and to withdraw the rejection under 35 U.S.C. § 103.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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